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Biomimetic Cationic Polyannulation Reaction Catalyzed by $Bi(OTf)_3$: Cyclization of 1,6-Dienes, 1,6,10-Trienes, and Aryl Polyenes

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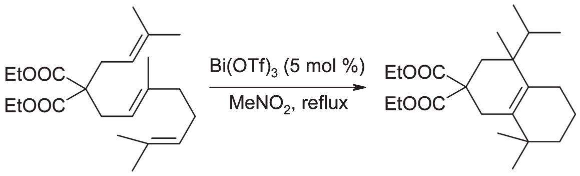
ABSTRACT



Nonactivated trienes and aryltrienes were cyclized into polycyclic compounds in good to excellent yields under bismuth triflate catalysis in a biomimetic fashion. The reaction showed broad applicability and allowed for the formation of functionalized bicyclic to tetracyclic structures from simple precursors in one pot. For some specific substrates, the cyclization was followed by a methyl shift as encountered in terpenoid biosynthesis.

Polyene cyclization reactions, aimed at mimicking terpenoid cyclase-catalyzed biosynthetic pathways to cyclic terpenoids in plants,[1] have been a rewarding matter of interest primarily devoted to the understanding of cation-π based cyclization mechanisms, rearrangements, and stereochemistry.[2] Such cationic-based cyclizations were further used as a powerful tool for the construction of polyannulated compounds in steroid syntheses, promoted by the stoichiometric use of BF_3-EtO_2, $SnCl_4$,[3] $MeAlCl_2/Me_2AlCl$,[4] or $Et_2SBr-SbCl_5Br$,[5] for example. Strong protic acids such as FSO_3H[6] or $ClSO_3H$[7] could also be used as stoichiometric promoters in such cyclizations. The first enantioselective polyene cyclization was reported in 1999, with the design of a reagent guided by the concept of Lewis acid assisted Bronsted acid (LBA), and applied to the synthesis of the benchmark odorant (−)-ambrox through the cyclization of (*E*,*E*)-homofarnesol promoted by 1 equiv of $SnCl_4$ associated with monomethylated (*R*)-BINOL.[8] Several applications of chiral LBAs in the mediation of polyene cyclization followed.[9]

To our knowledge, the metal-catalyzed cyclization of nonconjugated trienes or higher order unsaturated substrates has not yet been described.[10] To date, metal-catalyzed reactions involving cationic-type polyene cyclizations have

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only been reported for transformations involving the ring closure of non-conjugated dienic systems in which the cyclization was initiated by an activated function (epoxide, keto ester, or other reactive functional groups).[11]

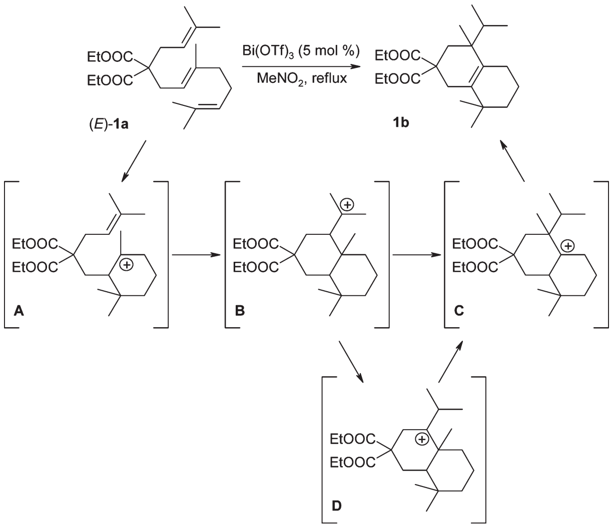
Whereas catalytic cycloisomerization processes involving enynes or diynes with organometallic complexes (mainly Pd, Au, Ru) have been extensively reported in recent years,[12] the catalytic cycloisomerization of non-conjugated olefins is rare because of the lower reactivity of the double bonds, in particular in highly substituted and bulky olefinic systems.

We have been interested in the preparation of Lewis superacids such as metallic triflates and triflimidates[13] and their use as catalysts for the functionalization of non-activated olefins,[14] α-amidoalkylation of carbon-centered nucleophiles,[15] Friedel–Crafts-type allylations,[16] as well as 1,6-diene cycloisomerisations.[17]

During our previous studies on 1,6-diene cycloisomerizations, $Sn(NTf_2)_4$, used at 2–5 mol %, was identified as an efficient catalyst, both in terms of yield and substrate scope, over a series of metallic triflates and triflimidates.[17] In the present contribution, we have extended our studies to cationic cyclization of non-conjugated trienes such as diethyl 2-geranyl-2-prenylmalonate **1a**, chosen as a model substrate (Scheme 1). $Sn(NTf_2)_4$, used at 5 mol %, resulted in a moderate 42% yield of the bicyclic product **1b**. Interestingly, a double cyclization occurred, presumably via intermediates **A**–**D** with the additional 1,2-methyl shift from the bridgehead carbon of intermediate **B** toward the vicinal position as in **C**. This rearrangement is similar to what is observed in terpenoid chemistry, in particular in the 1,2-methyl shift of eudesmyl carbocation[18] and in the overstoichiometric $BF_3 \cdot OEt_2$-mediated rearrangement in the labdane series.[19] Elimination compounds from **A** and **B** could be isolated from the reaction of **1a** under milder conditions (see the Supporting Information).

A screening of several metallic triflates and triflimidates, including Sn^{IV}, Sc^{III}, Al^{III}, Fe^{III}, or Cu^{II} derivatives, revealed that commercially available $Bi(OTf)_3$, a hydrated salt,[20] afforded the best activity and selectivity in terms of yield and catalytic activity for the tandem cyclization/rearrangement of **1a** affording **1b** in up to 78% yield.

Scheme 1. Double Cylization of (*E*)-**1a** Catalyzed by $Bi(OTf)_3$



It is unusual to observe Bi^{III} compounds exhibiting a π-Lewis character,[21] while they are commonly used as σ-Lewis acids.[22] The efficient results obtained with $Bi(OTf)_3$ for the cyclization of **1a**, and its apparent superiority over $Sn(NTf_2)_4$, prompted us to evaluate its catalytic activity in polyene cycloisomerizations. Particular attention was paid to the structural requirements in the substrate choice, the influence of a *gem*-diester moiety, or the possibility of involving an aryl group in the cyclization. $Bi(OTf)_3$ displayed good efficiency for this cyclization and functionalized polycycles were obtained in good yields (Table 1); its additional interest with respect to $Sn(NTf_2)_4$ being the use of a less toxic Lewis acid.[23] In the series of polyunsaturated compounds examined, a remarkable efficiency in the synthesis of bicyclic (entries 1–5), tricyclic (entries 6–8), and tetracyclic stuctures (entry 9) was attained.

Changing the prenyl side chain of **1a** into a crotyl side chain such as in **2a**, still associated with the geranyl moiety, resulted similarly in a double cyclization/methyl migration and led to **2b** (entry 2). The methyl rearrangement as observed in the cycloisomerization of **1a** also occurred with analogous structures **3a** and **4a**. The replacement of a

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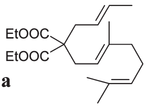
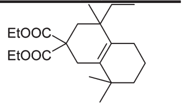
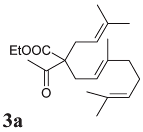
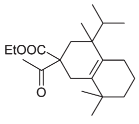
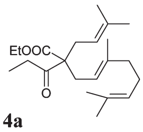
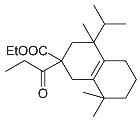
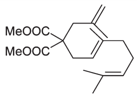
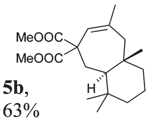
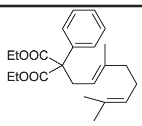
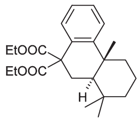
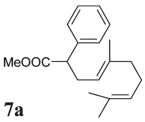
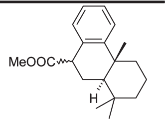
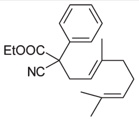
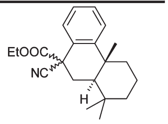
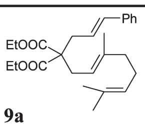
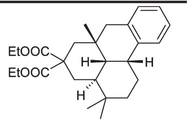
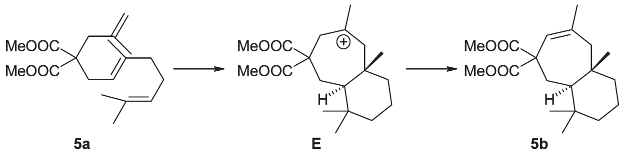
Table 1. Polyene Cyclizations Catalyzed by Bi(OTf)$_3$^{a}

Entry	Substrate	Time (h)	Products, Isolated yield
1	**1a**	0.4	**1b**, 78% (72)
2	 **2a**	0.08	 **2b**, 84% (81)
3	 **3a**	0.4	 **3b**, 65% dr 6/4 (36)
4	 **4a**	0.4	 **4b**, 66% dr 7/3 (58)
5	 **5a**	0.4	 **5b**, 63% 1 diastereomer (43)^c
6	 **6a**	0.1	 **6b**, 90% 1 diastereomer (76)
7	 **7a**	0.4	 **7b**, 90% dr 65/35 (74)
8	 **8a**	4	 **8b**, 90% dr 64/36 (75)^c
9	 **9a**	4	 **9b**, 99% 1 diastereomer (83)^c

^{a}General conditions: substrate (1 mmol), Bi(OTf)$_3$ (5 mol %), in anhydrous refluxing nitromethane (5 mL). ^{b}GC−FID yields determined with hexadecane as standard, isolated yields after column chromatography in parentheses. ^{c}Structure confirmed by X-ray spectroscopy.

prenyl by a methallyl unit as in **5a** led to the *trans*-fused bicyclo[5.4.0] compound **5b** in 63% yield without rearrangement, as confirmed by X-ray analysis (see the Supporting Information). According to our results, the requirements for such migration are (1) the formation of intermediates featuring a methyl group at the position 3 relative to the carbocation as in structure **B** (Scheme 1) and (2) connection of the carbon atom bearing the positive charge to the ring by a bond for which free rotation is possible. Free rotation indeed allows for a perfect alignment of the unoccupied atomic orbital of the carbocation and the σ-orbital of the C−H bond of the migrating substitutent. If free rotation is not possible, as with intermediate **E** from substrate **5a**, where the charge is formed within the 7-membered ring, the migration does not occur and a proton is simply eliminated leading to **5b** (Scheme 2).

Scheme 2. Cyclization of (*E*)-**5a** Does Not Feature the Methyl Shift



Interestingly, in the presence of a remote aryl group, a tandem diene or triene cyclization followed by a Friedel−Crafts-type cyclization occurred, affording the corresponding arene polycycles in excellent yields of 90−99% (entries 6−9).

Compounds **6b**−**8b** were obtained in good yields (90%) within short reaction times. The presence of a quaternary carbon on the tether, often advocated to facilitate the cyclization process through a Thorpe−Ingold effect,[24] was not necessary, since **7a** was efficiently converted into **7b** in good yield and short reaction time.

Substrate **9a**, presenting the structural features to undergo the methyl shift described above, indeed led to the rearranged polycycle **9b** in excellent yield (99%) and with total stereoselectivity in the creation of three C−C bonds in one single operation involving a methyl shift and several proton shifts. The structure of **9b** was also confirmed by X-ray spectroscopy (see the Supporting Information).

Following the Stork−Eschenmoser paradigm, *E*-olefins led to *trans*-fused rings with total selectivities, products **5b**, **6b**, and **9b** were obtained as single isomers, and structures were confirmed by X-ray crystallography. For substrates **3a**, **4a**, **7a**, and **8a**, the remote asymmetric carbon did not influence the creation of the additional asymmetric center and moderate dr's were obtained (6/4 to 7/3).

From a mechanistic viewpoint, the catalytic role of the metal ion versus the activity of TfOH formed by hydrolysis from residual water is still under debate.[25] The possibility of Bi(OTf)$_3$ forming hydrates or undergoing hydrolysis to free acid or hybrid species cannot be excluded. In the presence of 2,6-di-*tert*-butylpyridine as proton scavenger, or in the presence of molecular sieves 3 Å to trap residual water, the cycloisomerization was inhibited. On the other

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hand, running the reaction with **1a** in non-distilled CH_3NO_2 resulted in a slower reaction yielding 76% of **1b** after 1 h. However, and interestingly, when running the cyclization of **1a** with TfOH as the catalyst (5 mol %, conditions of Table 1), complete conversion was attained after 3 h and the yield of **1b** was of 48% because of degradation of the starting material in the presence of the strong Bronsted acid.

We propose that the catalytic cycloisomerization process might proceed via a Lewis acid assisted Bronsted acid-type activation (LBA),[9] in which water molecules coordinated to $Bi(OTf)_3$ would present a strongly enhanced but controlled acidity due to the presence of Bi^{III}. However, low steady state concentrations of TfOH formed upon $Bi(OTf)_3$ hydrolysis acting as catalyst could not be discarded. This feature of bismuth triflate has to be related to its structure. Triflates and triflimidates are indeed counterions with a particular behavior,[13c] different from what is observed with other counterions such as halides, for example. Likewise, structural data on hydrated bismuth triflate, although scarce, show that triflate anions and water molecules are located at a similar distance from the bismuth center, which undoubtedly resulted in increased acidity of water molecules.[26]

Theoretical studies of a related cycloisomerization of bis-homoallylic alcohols catalyzed by $Al(OTf)_3$ have shown that the coordination of the hydroxyl group of the substrate to the catalyst resulted in a strong enhancement of the acidity of the former.[27] If more water is added, the efficiency of the catalytic cycloisomerization system decreases and the yields and the selectivities drop. The catalytic system therefore needs the fine-tuning between $Bi(OTf)_3$ and H_2O, provided by bismuth triflate, for high efficiency. In the particular case of highly substituted olefins, the tandem cycloisomerizations reported here could be run in good yields simply with commercially available $Bi(OTf)_3$ as catalyst.

In summary, we describe herein efficient catalytic polyene cyclization system leading to differently functionalized polycycles in good to excellent yields, achieved through the use of a simple, nontoxic and readily available bismuth triflate catalyst, used in 5 mol %. This constitutes the first example of nonconjugated and nonfunctionalized polyene cyclization run with a catalytic amount of a Lewis acid. Tandem catalytic cyclization-Friedel–Crafts reactions were also efficiently performed. In several cases, selective methyl rearrangements involving 1,2-methyl shifts were observed in catalytic Lewis acid catalysis. As compared to other cationic-driven polyene cyclizations, no particular function but the olefin seems to be necessary to initiate the reaction. The cyclizations proceed smoothly in 63–99% yields, involving the formation of up to three cycles and three new C–C bonds in a single operation.

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Supporting Information Available. Detailed procedure and analytical data (^1H and ^{13}C NMR, MS and HRMS) for **1b**–**9b** and additional X-ray spectra for **5b**, **8b**, **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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